TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; or autoimmune neurological disorders. More particularly, the TNF antagonists or TNF blockers are used in a new treatment of these disorders by inhibiting the action of TNF in the cells of the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these neurological conditions.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease, immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression,

neuropathy, and pain; but also including cervical disc herniation, causing nerve compression in the neck; carpal tunnel syndrome and acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); autoimmune disease of the nervous system, and demyelinating diseases, the most common condition being multiple sclerosis.

Steroid drugs such as cortisone that are used to treat the aforementioned neurological problems and conditions are particularly hazardous because they are used either at high dosage, with a corresponding increasing risk of side effects, or because they are used chronically, also increasing their adverse effects. Lastly, steroids are only partially effective or completely ineffective.

There remains a need for a new pharmacologic treatment of these aforementioned physiological problems of the nervous system associated with autoimmune disease, demyelinating diseases, trauma, injuries and compression with the pharmacological use of TNF antagonists or TNF blockers, which are greatly beneficial for the large number of patients whom these conditions affect. Two new drugs which are powerful TNF blockers are etanercept and infliximab. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurologic damage mediated by TNF dependent processes occurring in the aforementioned neurological disorders. The use of these TNF antagonists or TNF blockers would

result in the amelioration of these physiological neurological problems.

DESCRIPTION OF THE PRIOR ART

Pharmacologic chemical substances, compounds and agents which are used for the treatment of neurological disorders, trauma, injuries and compression having various organic structures and metabolic functions have been disclosed in the prior art. For example, U.S. Patent Nos. 5,756,482 and 5,574,022 to ROBERTS et al disclose methods of attenuating physical damage to the nervous system and to the spinal cord after injury using steroid hormones or steroid precursors such as pregnenolone, and pregnenolone sulfate in conjunction with a non-steroidal anti-inflammatory substance such as indomethacin. These prior art patents do not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological trauma, injury or compression, or autoimmune neurologic disease as in the present invention.

U.S. Patent No. 5,605,690 to JACOBS discloses a method for treating TNF-dependent inflammatory diseases such as arthritis by administering a TNF antagonist, such as soluble human TNFR (a sequence of amino acids), to a human. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological trauma, injury or compression, or autoimmune neurologic disease, as in the present invention.

U.S. Patent No. 5,656,272 to LE et al discloses methods of treating TNF-alpha-mediated Crohn's disease using chimeric anti-TNF antibodies. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological trauma, injury or compression, or autoimmune neurologic disease, as in the present invention.

U.S. Patent No. 5,650,396 discloses a method of treating multiple sclerosis (MS) by blocking and inhibiting the action of TNF in a patient. This prior art patent does not teach the use of the TNF antagonist as in the present invention.

None of the prior art patents disclose or teach the use of the TNF antagonist or TNF blocker of the present invention for suppression and inhibition of the action of TNF in a human to treat neurological injury, trauma or compression, or autoimmune neurologic disease, in which the TNF antagonist gives the patient a better opportunity to heal.

Accordingly, it is an object of the present invention to provide a TNF antagonist for a new pharmacologic treatment of neurological disorders, trauma, injuries and compression affecting the nervous system of the human body, or autoimmune neurologic disease, such that the use of these TNF antagonists will result in the amelioration of these neurological conditions.

Another object of the present invention is to provide a TNF antagonist for providing suppression and inhibition of the action

of TNF in a human to treat neurological injury, trauma or compression, or autoimmune neurologic disease.

Another object of the present invention is to provide a TNF antagonist that reduces inflammation to the patient by inhibiting the action of TNF in the human body for the immediate, short term (acute conditions) and long term (chronic conditions), such that this reduction in inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment regimens for neurological conditions caused by neurological trauma, compression, injury and/or disease, such conditions including acute spinal cord injury, herniated nucleus pulposus (herniated disc), spinal cord compression due to metastatic cancer, carpal tunnel syndrome, pituitary adenoma, primary or metastatic brain tumors, chronic pain syndromes due to metastatic tumor, increased intracranial pressure, autoimmune demyelinating diseases such as multiple sclerosis, inflammatory CNS diseases, such as subacute sclerosing panencephalitis, and other related neurological disorders and diseases.

SUMMARY OF THE INVENTION

The present invention provides a method for inhibiting the action of TNF for treating neurological conditions in a human by administering to the human a dosage level of a TNF antagonist selected from the group consisting of etanercept and infliximab for reducing the inflammation of neuronal tissue of the human and/or

preventing immune system damage to neuronal tissue. The TNF antagonist is administered subcutaneously, intravenously, intrathecally, or intramuscularly.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

TNF antagonist regimens to be used for neurological disorders are designed in two general ways: acute regimens, designed to achieve rapid blood levels and rapid action, wherein TNF blockade is desired for hours to days; and chronic regimens, where TNF blockade is desired for days, weeks, or months. Currently available TNF antagonists which are suitable for these regimens are etanercept (ENBREL™) from Immunex Corporation and infliximab (REMICADE™) from Centocor, Inc. Trauma, injury, compression and other neurological disorders can affect individual nerves, nerve roots, the spinal cord, or the brain. The conditions which are of most concern here are the following:

1) acute spinal cord injury,

2) demyelinating diseases, such as multiple sclerosis,

3) herniated nucleus pulposus (herniated disc),

4) spinal cord compression due to metastatic cancer,

5) carpal tunnel syndrome (non-RA),

6) pituitary adenoma,

7) primary or metastatic brain tumors,

8) chronic pain syndromes due to metastatic tumor,

9) increased intracranial pressure, and

10) inflammatory CNS diseases, such as subacute sclerosing panencephalitis.

TNF antagonists are a novel way to treat neurologic trauma, injury, compression and neurological disorders in comparison with steroids. Experimental evidence has shown that excessive levels of TNF are released by injury to neuronal tissue. Accordingly, the use of TNF antagonists will result in amelioration of these neurological conditions. Because of the profoundly powerful action of the new TNF antagonists that have recently become available these agents can prevent neurologic injury in a unique way, filling an urgent clinical need for more effective therapy. Also, because of the extremely safe side effect profile of these agents, they can be used either singly or in combination with other pharmacologic agents. Specifically, TNF antagonists can safely be used with steroids, which are the only other class of agents which have been shown to be beneficial for certain of these conditions. Importantly, the TNF antagonists lack the adverse effects of steroids as previously described. Lastly, steroids are only partially effective or completely ineffective.

More detailed discussion of each of these clinical conditions is as follows:

1) Acute spinal cord injury:

About 10,000 cases occur per year in the U.S., with a current population of over 200,000 patients with residual neurologic damage, many of whom are paralyzed (quadriplegia or paraplegia). Current treatment for the acute injury is inadequate. In the early

1990's it was shown that early (within 8 hours of injury) treatment with high doses of steroids (methyl prednisolone) was beneficial for some of these patients. Surgical stabilization and spinal decompression is often necessary because of excessive swelling (edema) which can itself cause further severe injury to the cord due to further compression of the cord against its bony spinal canal. The etiology of most of these cases are motor vehicle accidents, with the remainder being sports injuries, falls,. and other accidents. The window of opportunity for treatment is small, since massive swelling can occur within minutes.

The treatment regimen used here would be the acute regimen. This could involve any of the TNF antagonists, but currently etanercept would be the leading candidate. Etanercept is currently approved only for rheumatoid arthritis, and is used as a subcutaneous injection of 25mg used twice a week. This regimen produces peak blood levels in an average of 72 hours. A preferred method for acute spinal cord injury involves intravenous infusion to produce more rapid serum levels and higher levels than achieved by SC injection. This is a new method of dosing that is not being used for arthritis. This acute regimen is a unique delivery method for etanercept and is uniquely necessary for clinical neurologic conditions requiring rapid blockade of TNF.

2) Herniated nucleus pulposus (herniated disc):

Low back pain affects 70% of the population during their lifetime, with 25% of this group having pain in the sciatic distribution. Current pharmacologic treatment is inadequate,

consisting of analgesics and anti-inflammatory medications (such as nonsteroidal anti-inflammatories (NSAIDS), such as ibuprofen (Motrin, etc.) and epidural steroid injections (generally regarded as having limited usefulness). Many of these patients eventually have surgery. Complications of lumbar disc herniation include permanent damage to the sciatic nerve, causing muscle weakness and atrophy in the lower extremity. Acute herniation with rapid onset of pain and sciatic nerve symptoms could be treated with the above acute regimen with or without addition of the chronic regimen (described below) if symptoms continued. Treatment could also be reserved for patients not responding to conventional therapy. The acute treatment regimen, as outlined above, could be used for patients in whom rapid control of symptoms was desired. Most patients, however, would be treated conservatively and conventionally at first, with TNF blockade using one of the chronic regimens below added later for nonresponders. Herniated cervical discs would be treated the same way as herniated lumbar discs with the need for careful evaluation by a neurologist, neurosurgeon, and/or orthopedic surgeon for signs of neurologic compromise kept in mind. The chronic treatment regimen includes subcutaneous etanercept of 25mg (dosage range 10mg to 50mg) once or twice a week; or infliximab administered by intravenous infusion once every two months (range once per month to once per six months).

3) Spinal cord compression due to metastatic cancer:

Cord compression due to metastatic cancer is a catastrophic event leading to rapid paralysis if not quickly diagnosed and

treated. It is most common with cancers of the breast, colon, lung and prostate, but can be a complication of metastatic disease from a wide variety of malignancies, including melanoma and multiple myeloma. Current treatment regimens include high dose steroids, emergency radiation treatment, and/or emergent surgical decompression. Paralysis can occur within hours, so treatment must be initiated within this time period to avoid permanent sequelae. The mechanism of action of TNF blockage here would be similar to that above. In addition, it is possible that TNF blockade could be directly tumoricidal or tumoristatic with certain malignancies. Impending cord compression could be treated with the chronic regimen. However, as explained above, most patients would need to be emergently treated with the acute regimen, as outlined above.

4) Carpal Tunnel Syndrome (CTS) (non-RA):

Carpal tunnel syndrome involves compression of the median nerve at the wrist, causing pain and neurologic symptoms in the hand. It is a common condition, being aggravated by repetitive stress injury (RSI) in the workplace (such as typists and writers, manual laborers, etc.), and is also a complication of rheumatoid arthritis (RA). Use of TNF blockade for carpal tunnel syndrome in patients with established RA would likely be covered by the existing arthritis medication for treating RA. But most patients with carpal tunnel syndrome do not have RA; they either have idiopathic CTS or CTS caused by RSI. CTS is a major cause of disability and responds poorly to current treatment regimens, which include NSAIDS, wrist splinting, and injection of steroids. The

chronic treatment regimen as outlined above would be used for the treatment of CTS (non-RA type).

5) Pituitary Adenoma:

Benign pituitary tumors grow adjacent to the optic chiasm. Unrestrained growth causes compression of the optic nerve, causing visual field defects and eventuating in blindness. Treatments include radiation, surgical decompression and bromocriptine. TNF blockade could prove to be a valuable adjunctive therapy, and could be either acute or chronic, depending on the clinical picture.

6) Primary or Metastatic Brain Tumors:

Primary brain tumors can be either benign (most commonly meningioma) or malignant (usually gliomas). Metastatic brain tumors can be from any source, most commonly lung cancer, breast cancer, or other malignancies such as melanoma. Treatment for these tumors is primarily surgery or radiation, with generally poor response to chemotherapy. Many of these tumors cause surrounding edema which can cause further neurologic deterioration. TNF blockade, either acute or chronic, could be beneficial while these patients are awaiting surgery. Additionally, TNF blockade, as discussed above, could have direct tumor inhibiting properties.

7) Chronic pain syndromes due to metastatic tumor:

Pain due to metastatic cancer is inadequately treated by currently used agents. It is probable that the mechanism of action of this pain is mediated in part by the overproduction of TNF. TNF blockade could be beneficial for selected tumors, particularly bone metastases where compression is involved. The chronic treatment

regimens would be used. One general note of caution when treating malignancies is necessary: While TNF blockade is likely to have an antitumor effect with certain malignancies, it is also possible that TNF blockade could increase growth rates with certain malignancies.

8) Elevated Intracranial Pressure (EICP):

EICP can be idiopathic (Pseudotumor cerebri) or caused by certain drugs (vitamin A excess, isotretinoin, tetracyclines, etc.) caused by malignancy (as above), or by benign tumors (e.g. cystercircosis). TNF blockade, either acute or chronic, could be helpful.

OPERATION OF THE PRESENT INVENTION

1) Chronic regimen dosing with etanercept

For adults the dose is 25mg subcutaneously (range 10mg to 50mg) administered in a range of twice a week to once a month. The initial regimen being 25mg subcutaneously twice a week and for children 0.4mg/kg given twice a week. Expected serum concentrations with this regimen would be about 3.0mcg/mL, with a desired range between 0.5 and 10mcg/mL. Other routes for chronic administration could include IM or IV dosing regimens.

2) Acute regimen dosing with etanercept

Acute treatment regimens include administration of etanercept by SC, IM, IV and intrathecal dosing routes for acute administration.

2A) Acute IV regimen with etanercept

Etanercept is administered by IV infusion in a quantity sufficient to produce a serum concentration in the range of 0.5mg/mL to 50mg/mL.

2B) Acute IM regimen for etanercept

Etanercept is given by intramuscular administration in a dose of 50mg having a range of 25mg to 100mg.

2C) Acute Intrathecal regimen with etanercept

There may be clinical use for etanercept in the cerebrospinal fluid, such as for treatment of CNS lesions (brain tumors, cord compression). Intrathecal therapy means introducing the TNF antagonist into the cerebrospinal fluid of the patient. The exact dosage is on the order of 10mg (range 1mg to 50mg).

3) Chronic treatment regimen with infliximab

Chronic indications for infliximab include herniated nucleus pulposus (herniated disk), carpal tunnel syndrome, pituitary adenoma, demyelinating disease, primary or metastatic brain tumors and chronic pain syndromes due to metastatic tumor.

Usual dosage for infliximab is 5mg/kg given by IV infusion every two months with a range of 2.5mg/kg to 20mg/kg given every 2 weeks to 2 months.

4) Acute treatment regimen with infliximab

Acute indications for infliximab include acute spinal cord injury, acute demyelinating disease, spinal cord compression and increased intracranial pressure.

The dosage for infliximab used for the acute regimen is 10mg/kg administered by IV infusion once (range 2.5mg/kg to 25mg/kg). For acute spinal cord injury only the intrathecal administration of infliximab is 0.3mg/kg having a range of 0.1mg/kg to 1mg/kg.

5) Treatment with existing regimens

The treatment regimens of the present invention may be used in conjunction with or in place of existing treatments, such as steroids and surgery. When the treatment regimens of the present invention are used concurrently with currently available treatments, the results are additive and therefore beneficial.

ADVANTAGES OF THE PRESENT INVENTION

Accordingly, an advantage of the present invention is that it provides a TNF antagonist for a new pharmacologic treatment of neurological disorders, trauma, injuries and compression affecting the nervous system of the human body, or autoimmune neurologic disease, such that the use of these TNF antagonists will result in the amelioration of these neurological conditions.

Another advantage of the present invention is that it provides for a TNF antagonist for providing suppression and inhibition of the action of TNF in a human to treat neurological injury, trauma or compression, or autoimmune neurologic disease, or inflammatory disease of the nervous system.

Another advantage of the present invention is that it provides a TNF antagonist that reduces and prevents further neurological inflammation to the patient by inhibiting the action of TNF in the

human body for the immediate, short term (acute conditions) and long term (chronic conditions), such that this reduction and prevention of inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment regimens for neurological conditions caused by neurological trauma, compression, injury and/or disease, such conditions including acute spinal cord injury, herniated nucleus pulposus (herniated disc), spinal cord compression due to metastatic cancer, carpal tunnel syndrome (non-RA), demyelinating disease, pituitary adenoma, primary or metastatic brain tumors, chronic pain syndromes due to metastatic tumor, increased intracranial pressure, and other related neurological disorders and diseases.

Another advantage of the present invention is to provide a TNF antagonist to treat neurologic disorders in humans either acutely or chronically by blocking the action of TNF and thereby modulating the immune response affecting neuronal tissue.

A latitude of modification, change, and substitution is intended in the foregoing disclosure, and in some instances, some features of the invention will be employed without a corresponding use of other features. Accordingly, it is appropriate that the appended claims be construed broadly and in a manner consistent with the spirit and scope of the invention herein.